SYNTHESIS OF 1-ETHYL-2-METHYL-4-NITROIMIDAZOLE-5-THIOL

BY

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A PROJECT WRITTEN IN THE DEPARTMENT OF CHEMISTRY AND SUBMITTED TO THE FACULTY OF PHYSICAL SCIENCES IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE AWARD OF DEGREE OF B.SC INDUSTRIAL CHEMISTRY OF THE UNIVERSITY OF BENIN, BENIN CITY, EDO STATE, NIGERIA.

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CERTIFICATION

We the designated certify that this project work was carried out and presented by Ufoma Grace ONOWHO (Miss) in partial fulfilment of the requirement for the award of Bachelor of Science degree (B.Sc.) Chemistry, in the Department of Chemistry, University of Benin, Benin City, Edo State.

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PROF J.B OWOLABI DATE

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HEAD OF DEPARTMENT

DEDICATION

I dedicate this project work to God Almighty for his infinite favors, strength and grace to pull through and to my parent Mr. and Mrs. ONOWHO in for their support prayers and assistance.

ACKNOWLEDGEMENT

My greatest gratitude goes to God Almighty, the infinity of goodness, from whom every good gift comes, for the gifts of life and knowledge and who permitted the success and completion of this report.

I also want to express my gratitude to all professors, lecturers and staff in the Department of Chemistry whose efforts in producing great leaders of tomorrow will never be in vain. Particularly I express my gratitude to my supervisor, PROFESSOR B.J. OWOLABI who made this project work a success through his encouragement, patience and support.

I also express my profound gratitude to my parent Mr and Mrs JOHN ONOWHO and also to my siblings whose prayers and support went a long way in the success of this project work and during my course of study in the University of Benin.

I want to specially appreciate Mr H.C. Ndibe for his support and encouragement in the achievement of this project work.

My gratitude to my friends especially Ike Maryjovian, Njoku Ebere, Azubuike Favour, my roommate, Nwabuzor Blessing and my well-wishers, and my project colleague for their encouragements and prayers during this research project work and my stay in the university ,may Almighty God bless and protect every one of them in all that they do, Amen.

ABSTRACT

This research study aimed to produce 1-ethyl-2-methyl-4-nitroimidazole-5-thiol. Initially, N,N-diethyloxamide (Compound 1) was created through the reaction between diethyloxalate and ethylamine. Following this, 5-chloro-1-ethyl-2-methylimidazole (Compound 2) was formed by treating N,N-diethyloxamide with phosphorus pentachloride. Compound 2 underwent nitration to produce 5-chloro-1-ethyl-2-methyl-4-nitroimidazole. The subsequent reaction of Compound 3 with thiourea resulted in the formation of 1-ethyl-2-methyl-4-nitroimidazole-5-thiol. The purity of the compounds was assessed using thin-layer chromatography, recrystallization, and melting point determination methods.

CHAPTER ONE

1.0 INTRODUCTION AND LITERATURE REVIEW

1.1 INTRODUCTION

Heterocyclic compounds are organic molecules characterized by a ring structure that incorporates at least one element, such as nitrogen (N), oxygen (O), or sulfur (S), within the cycle. While there is a wide array of heterocyclic compounds, some contain fewer than five or six atoms. These compounds can exhibit both aromatic and non-aromatic ring structures. Many non-aromatic heterocyclic molecules exhibit similar chemical properties to acyclic compounds. For instance, cyclic ethers resemble ethers, and cyclic secondary amines resemble linear secondary amines, as observed in various examples (Hans et al., 2003).

A single cycle or many cycles, which can be isolated or condensed, may be present in heterocyclic compounds. Heterocycle-condensed compounds with carbon aromatic cycles are also prevalent. Hetarenes (PHAs) are a term sometimes used to refer to polycyclic aromatic compounds that contain heterocycles. Similar to other organic compounds, physical qualities are a significant criterion for evaluating the purity of heterocycles. Heterocycles exhibit the same high degree of uniformity in their physical characteristics as other organic molecules. The melting point was previously a commonly used purity criteria, but it has been progressively replaced by other purity indicators, such as optical spectra, based on light absorption, mass spectra based on relative masses of molecular fragments. However, understanding melting and boiling temperatures is still useful for determining a compound's purity (Thomas *et al.*, 1997).

1.1.1 BACKGROUND OF STUDY

Imidazole have a unique position in heterocyclic chemistry, and in recent years, interest in their derivatives has grown significantly due to their many useful pharmacological and chemical properties. Imidazole is frequently utilized as a catalyst in a number of significant chemical reactions, including the creation of polymers, plastics, and different organic compounds. It is a significant molecule, as evidenced by the wide range of industries in which it is used, making it a crucial element in pharmaceutics as well as a key building block in organic synthesis. An organic substance with the chemical formula $C_3H_4N_2$ is imidazole. It is a five-membered heterocyclic aromatic molecule with a ring structure that contains two nitrogen atoms. Imidazole is a versatile substance that can be found in a variety of organic goods (Verma *et al*., 2013).

Its atmosphere is full of electrons and has remarkable structural characteristics. Due to its exceptional qualities, the pharmaceutical industry has conducted substantial research and used it to develop a number of medications. Imidazole-based medications demonstrate a wide range of bioactivities due to the variety of therapeutic targets, enzymes, and receptors they interact with in biological systems. Particularly, numerous imidazole-based compounds have made significant strides in medicinal chemistry and are now available as highly effective clinical medications to treat a variety of malignancies. Numerous fungicides, antifungal, antiprotozoal, and antihypertensive drugs contain synthetic imidazole. Imidazole is found in tea leaves and coffee beans, that stimulates the central nervous system (Leon *et al.*, 2007).

Imidazole is synthesized for a variety of reasons, including: Imidazole and its derivatives function as adaptable building blocks in organic synthesis to support chemical research. Imidazole is a helpful tool in organic chemistry due to its capacity to function as a nucleophile, base, or ligand, which enables a variety of chemical transformations. They are used in the synthesis of heterocyclic and other complicated molecules. Because its derivatives are used in a variety of industrial fields, imidazole is also synthesised.

Imidazolium salts, for instance, can be used as green solvents in the pharmaceutical, polymer, and materials science sectors or as an ionic liquid for catalysis. The fact that imidazole is a fundamental molecule with intriguing physicochemical characteristics and reactivity should be understood (Ebet *et al.*, 2002).

By synthesizing different imidazole derivatives with minor structural derivatives, it is possible to determine the structural – activity relationship, scientists can investigate the relationship between the compound's structure and its biological activity. This enables the identification of special features necessary for optical biological activity and can guide the design of more effective drugs. Synthesizing imidazole allows researchers to investigate its behaviour under different conditions and its interactions with other compounds contributing to the understanding of organic chemistry (Hochachka *et al.*, 2002).

1.1.2 OCCURRENCE AND HISTORY OF IMIDAZOLE

Histidine, a vital amino acid, along with vitamin B12, an essential component of DNA, and purines, histamine, and biotin, which are crucial for human health, all contain an imidazole nucleus as their primary structural component. Examples of natural or synthetic medicinal compounds containing this nucleus include cimetidine, azomycin, and metronidazole. Imidazole was first synthesized by Heinrich Debus in 1858, although several derivatives had already been discovered by the 1840s. Debus created imidazole by combining glyoxal and formaldehyde with ammonia, a method still used despite its relatively low yields, particularly for producing C-substituted imidazoles (Ramachandran et al., 2011).

Imidazole is a planar five-membered ring that is soluble in polar solvents like water. It exists in two tautomeric forms due to the hydrogen atom's placement on either of the two nitrogen atoms. Imidazole exhibits complete solubility in water and possesses a strong polarity with an estimated dipole moment of 3.61D. Its amphoteric nature allows it to act as both an acid and a base. The compound's aromatic classification is due to the presence of a sextet of π-electrons, comprising two electrons from the protonated nitrogen atom and one from each of the other four atoms in the ring (Singh et al., 2008).

The scheme below illustrates various resonance structures of imidazole.

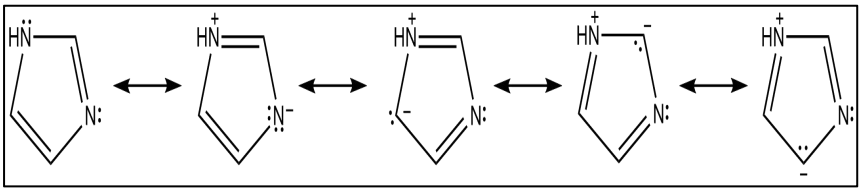


Fig 1: Resonance structures of imidazole

The chemical compound known as imidazole is represented by the formula C3H4N2. It appears either colorless or white and readily dissolves in water, resulting in a slightly alkaline solution. Imidazole is classified as an aromatic heterocycle in the field of chemistry and falls under the adiazole category, with non-contiguous nitrogen atoms in meta-substitution. Many medications, such as specific antifungals, antibiotics belonging to the nitroimidazole class, and the sedative midazolam, contain an imidazole ring. When combined with a pyrimidine ring, imidazole yields a purine, which is the most prevalent nitrogen-

containing heterocycle found in nature. The term "imidazole" was coined by the German chemist Arthur Rudolf Hantzsch (1857–1935) in 1887.

1.1.3 PROBLEM STATEMENT

The repeated use of imidazole- based agrichemicals in the agricultural industry has lead to the development of resistance in target pathogens and pests. This resistance has greatly reduced the effectiveness of the chemicals over time. The development of an alternatively more sustainable pest and disease management strategies is a growing trend in agriculture. Imidazole-based agrichemicals may face competition from biological control methods and less toxic chemical options.

Thus, due to the need to synthesize an imidazole-based derivative which has a low resistance in pathogens and pests, this method of synthesis is employed. The synthesis also aims to achieve a higher yield, purity and an efficient and cost-effective method of production of imidazole.

1.1.4 JUSTIFICATION OF RESEARCH WORK

The synthesis method employed has an esteemed history in organic chemistry and has contributed significantly to the understanding and development of synthetic organic chemistry. Wallach′s synthesis provides valuable mechanical insights into the formation of the imidazole organic molecules as compared with other method of synthesis of imidazole.

Thus, the study of the reaction pathways and intermediate has led to a deeper understanding of organic chemistry principles. This synthesis is very instrumental in the discovery of new products and the elucidation of their chemical structures. For this reason, it is a highly suggested method of synthesis, as it serves as a foundation for innovation and further development in organic chemistry (Maurizo *et al*., 2023).

1.1.5 SCOPE OF WORK

This study focuses on the synthesis of 1-ethyl-2-methyl-4-nitroimidazole-5-thiol.

1.1.6 AIM

The aim of this research is to synthesize 1-ethy-2-methyl-4-nitro imidazole 5-thiol

1.1.7 OBJECTIVES

To achieve this aim, the following objectives were attained;

- Synthesis of N,N-diethyloxamide
- Synthesis of 5-chloro-1-ethyl-2-methylimidazole
- Synthesis of 5-chloro-1-ethyl-2-methyl-4-nitroimidazole
- Synthesis of 1-ethyl-2-methyl-4-nitro-imidazole-5-thiol

1.2 LITERATURE REVIEW

1.2.1 Synthesis of imidazole

In 1858, Heinrich Debus pioneered the production of imidazole by reacting glyoxal with formaldehyde in an ammonia solution, initially known as glyoxaline. Despite its seemingly simple structure, imidazole possesses a remarkable chemical complexity. It serves as a core component that offers abundant chemical diversity due to its ease of construction and functionalization. Imidazole plays a crucial role in vital biological processes, such as catalyzing enzymatic reactions essential for sustaining life. Numerous studies have highlighted the wide-ranging therapeutic potential of imidazole-based compounds. These include antibacterial, anti-inflammatory, anti-diabetic, anti-parasitic, anti-tuberculosis, antifungal, antioxidant, antitumor, anti-malarial, anticancer, and antidepressant properties (Verma et al., 2013). This diverse array of bioactive compounds suggests promising avenues for the development of new treatments and therapeutic strategies.

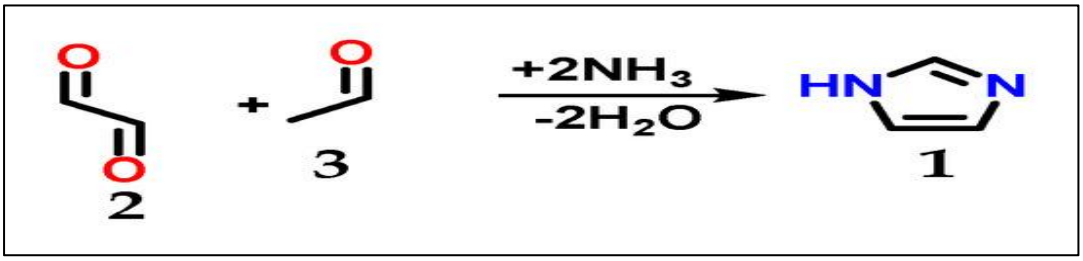


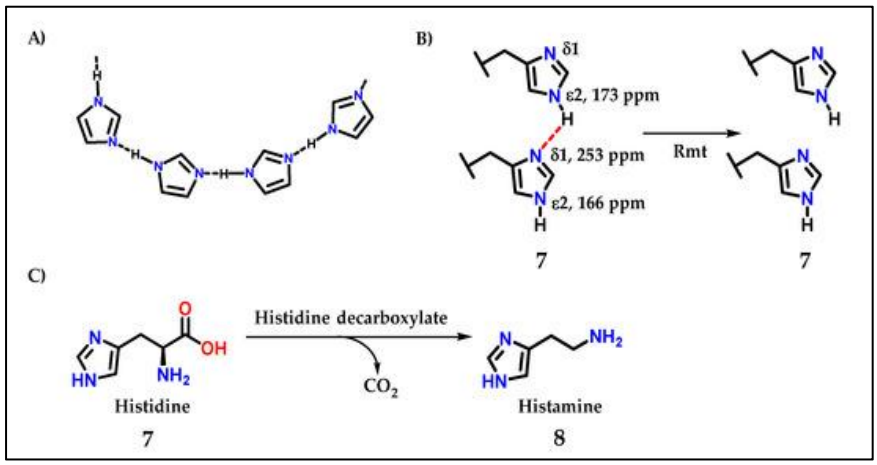
Fig 2. Synthesis Method for Imidazole Utilizing Glyoxal, Formaldehyde, and Ammonia

Imidazole possesses a flat 5-membered ring structure and dissolves readily in polar solvents such as water. Its hydrogen atom can be situated on either of its two nitrogen atoms, resulting in the identification of two similar tautomeric structures. Imidazole is highly polar and exhibits properties of both an acid and a base, thus being classified as an amphoteric compound. Its aromatic character is attributed to the presence of a sextet of electrons, including two nonbonding electrons from nitrogen N-1 and one from each of the remaining four ring atoms.

Imidazole can react with strong acids to generate stable crystalline salts known as imidazolium salts by protonating the sp2 nitrogen (N-3). With a pKaH of 7.1, imidazole functions as a potent base. Because both nitrogen can contribute equally in charge

accommodation thanks to the amidine-like resonance, imidazole has a higher basicity than pyridine 4 (pKaH of 5.2). Comparatively, the basicity of imidazole contrasts with that of pyrrole, which has a pKaH of 0.4 and is a very weak base due to the loss of aromaticity that results from protonation and is supported by the nonbonding electron pair of N-1 nitrogen.

Figure 3: (A) Intermolecular interactions facilitated by hydrogen bonding in imidazole-containing derivatives. (B) Intermolecular interactions occurring in histidine residues. (C) Configuration of histidine, the precursor for histamine production (Mullins et al., 2007).

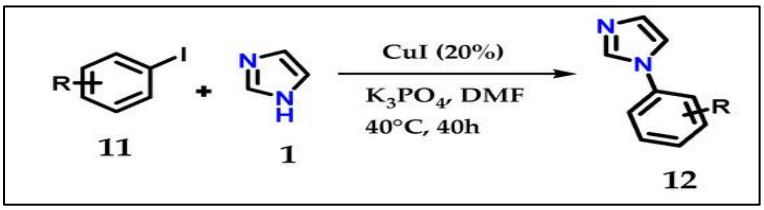


Imidazole demonstrates notable efficacy as both a hydrogen bond donor and acceptor. In scenarios where an interaction requires a hydrogen donation, the N-1 nitrogen, being more acidic, provides its hydrogen. Conversely, the sp2 nitrogen (N-3) acts as a hydrogen acceptor in such interactions. This characteristic plays a pivotal role in the mechanisms of action of various enzymes employing the imidazole ring, including the histidine amino acid residue, a fundamental component of proteins. Both small bioactive molecules and larger macromolecules rely on these vital interactions, which are integral to biological processes.

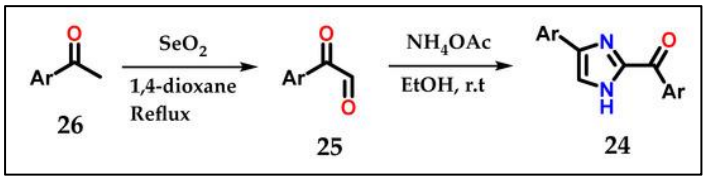
1.2.2 Functionalization of imidazole

The functionalized structures of imidazole are useful building blocks for the synthesis of biological, chemical and pharmaceutical interests.

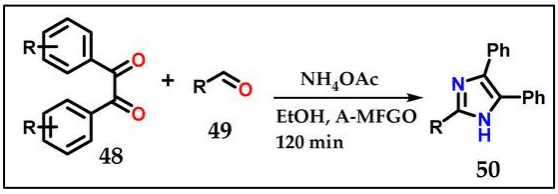
- Mono-Substituted Derivatives (Zhu *et al.*, 2009)



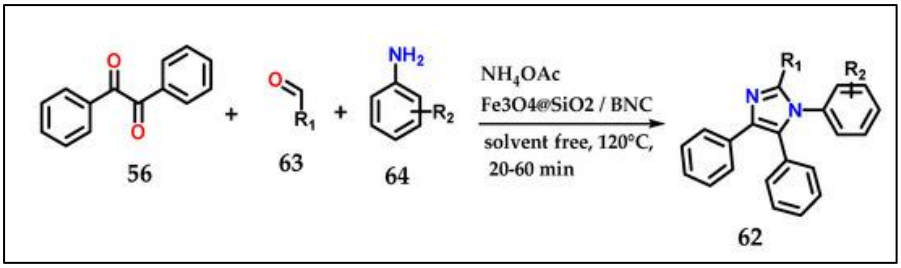
- Di-Substituted Derivatives (Kuzu *et al.*, 2017)



- Tri-Substitued Derivatives (Singh *et al.*, 2018)



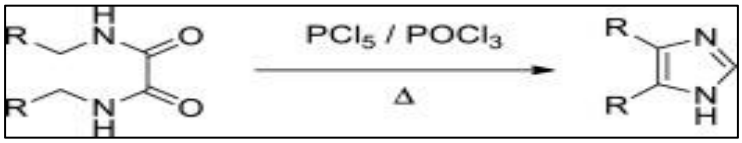
- Tetra-Substituted Derivatives (Ali *et al.*,2015)



1.3 IMIDAZOLE DERIVATIVES AND THEIR SYNTHESIS

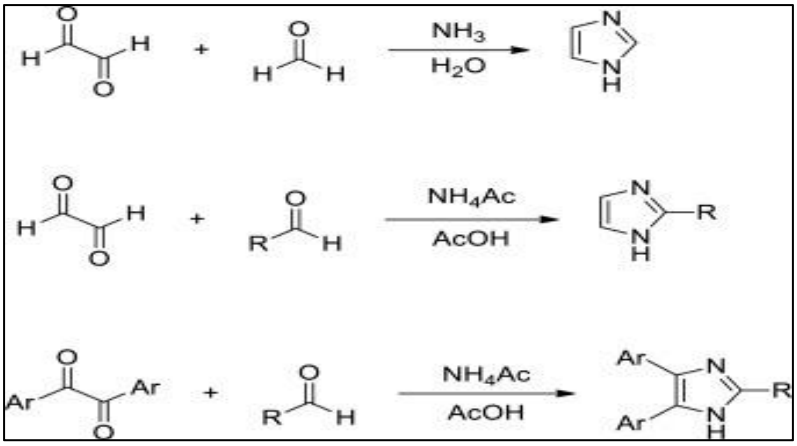
1.3.1 Wallach's synthesis:

It involves the cyclization of N,N′-disubstituted oxamides, resulting in the formation of 1-substituted 5-chloroimidazoles through a reaction with phosphorus pentachloride. (Benincori et al.), 2010)



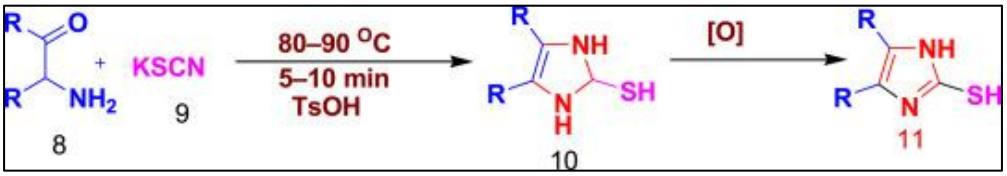
1.3.2 Debus-radziszewski synthesis:

The Radziszewski synthesis represents a traditional approach for producing imidazole and its various derivatives, including mono-, di-, and tri-substituted imidazole. This method involves the condensation of 1,2-dicarbonyl compounds, such as α-ketoaldehyde or α-ketoketone, with aldehyde in the presence of NH3/H2O or NH4 Ac/AcOH mixtures. (Ebel *et al.*, 2002)



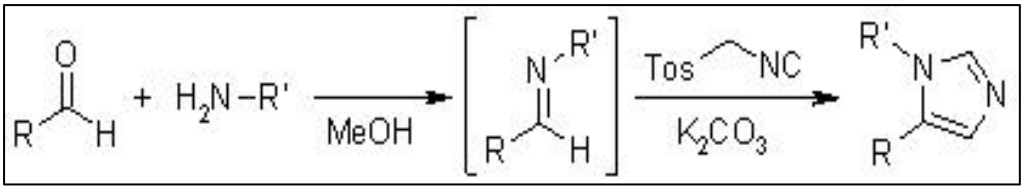
1.3.3 Marckwald synthesis:

The Marckwald synthetic approach involves the intriguing process of creating 2-mercaptoimidazoles from α-amino ketones in order to produce imidazoles substituted with 2-thiol groups.



1.3.4 Van leusen synthesis:

In 1975, Van Leusen successfully produced 1,5-disubstituted imidazole derivatives by reacting tosyl methyl isocyanide with aldimines under basic conditions. This reaction occurred in the presence of K2CO3 in a mixture of methanol/dimethylformamide-tosylic acid (MeOH/DMF-TsOH) at a temperature of 20 °C. The yield of 1,5-disubstituted imidazole derivatives achieved through this method was 82%.



The four standard methods listed above are the most effective ones for synthesising poly-functionalized imidazole derivatives. Different contemporary methods have been established for the synthesis of imidazole scaffolds with high functionalization (Zheng et al., 2020).

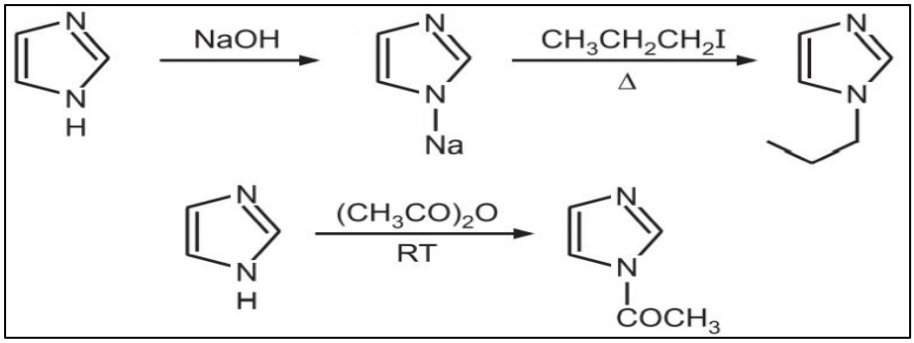
1.4 REACTIONS OF IMIDAZOLE

1.4.1 Electrophilic substitution reaction of imidazole:

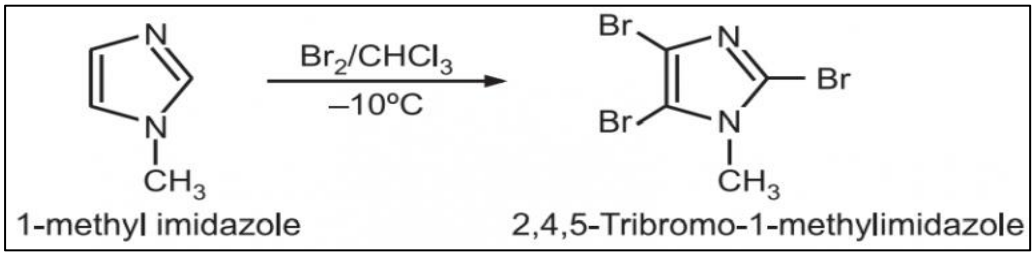
The heterocycle imidazole has an excess of π electrons. Nucleophilic substitution happens at C(2), while electrophilic substitution typically happens at C(4) or C(5). Imidazole > thiazole > oxazole is the order of reactivity for electrophilic substitution of azoles.

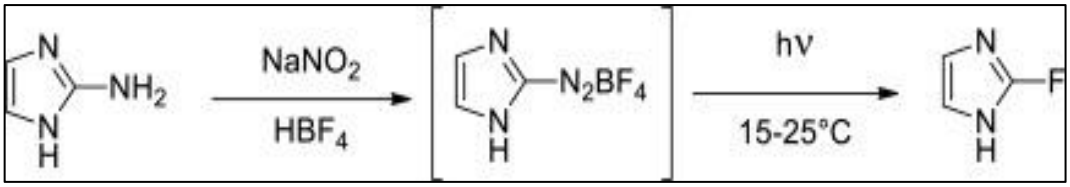
Electrophilic Substitution Reaction

1.4.1.1 N-alkylation and N-acylation:



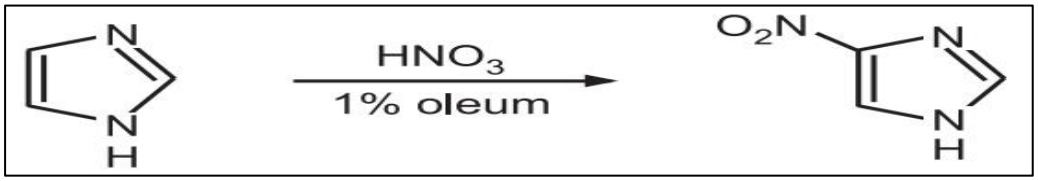
1.4.1.2 Halogenation:



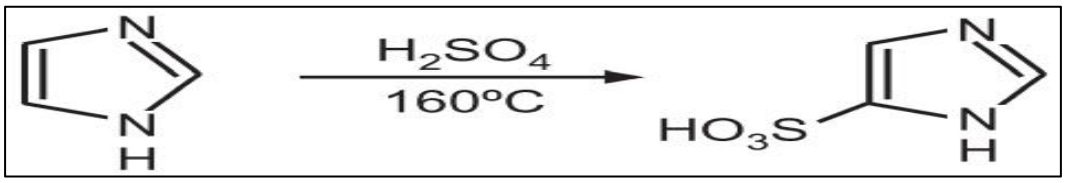


2-Aminoimidazole undergoes diazotization reaction with $NaNO_2$ and HBF_4 *at -5°C to -10°C to yield imidazole diazonium fluoroborate intermediate after irradiation gives 2-fluoroimidazole as the final product.*

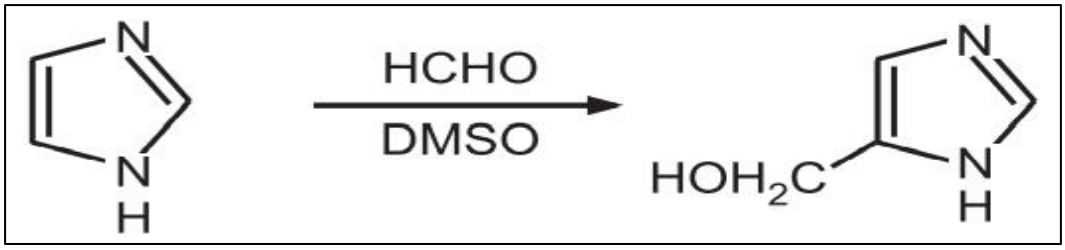
1.4.1.3 Nitration:



1.4.1.4 Sulfonation:

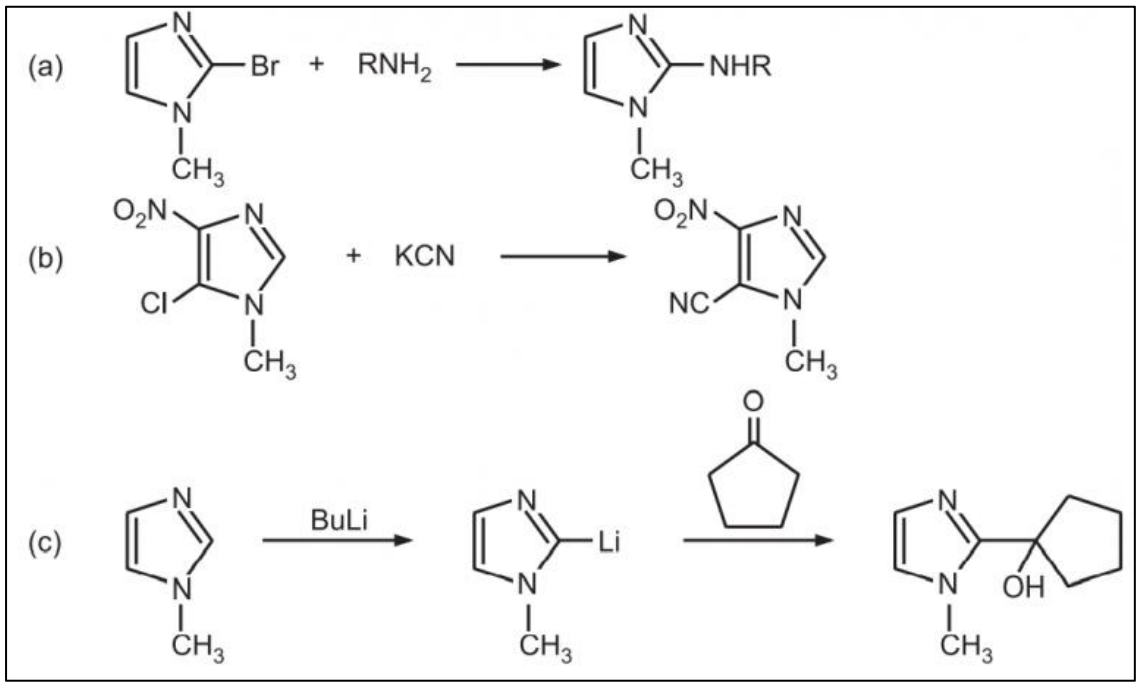


1.4.1.5 Reaction with aldehydes and ketones: N-unsubstituted imidazole is treated with formaldehyde (HCHO) in the presence of dimethyl sulphoxide (DMSO), which causes hydroxymethylation at the C4 position.



1.4.2 Nucleophilic substitution reaction of imidazole:

If electron-withdrawing groups are present, nucleophilic substitution at the C(2)-position of imidazole is easily triggered. For instance, 2-haloimidazoles go through nucleophilic substitution processes in which a nucleophile takes the place of the halogen.



1.4.3 Action of oxidizing agents:

Imidazole remains resistant to auto-oxidation and the effects of chromic acid; however, it is susceptible to attack by hydrogen peroxide or perbenzoic acid.

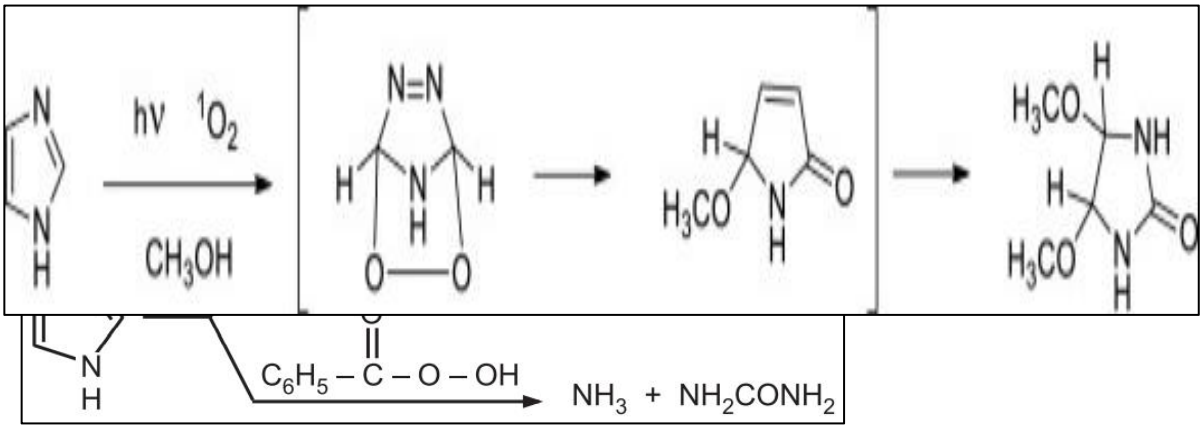
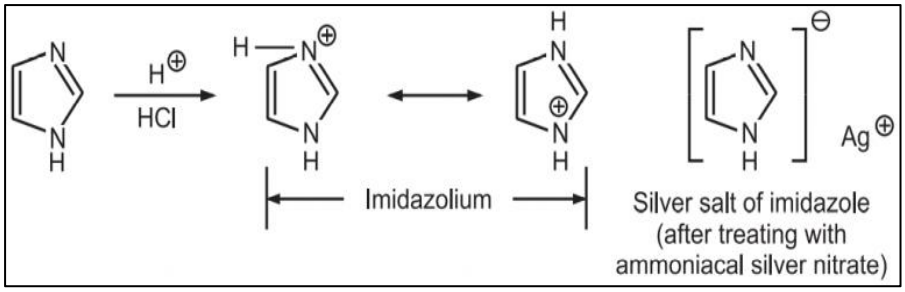


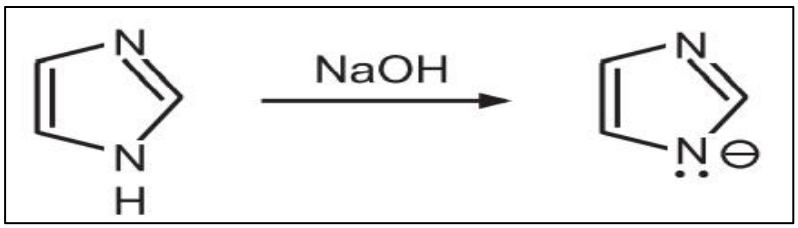
Photo-oxidation occurs when imidazole experiences photosensitized oxidation with the presence of singlet oxygen. This process leads to the formation of imidazolidin-2-one, passing through a cyclic peroxide intermediate.

1.4.4 Reaction with acids:

Imidazole readily creates durable crystalline salts when strong acids protonate its N3-atom.



Conversely, imidazole can function as an acid and a strong base can take the proton from the N1 atom. Imidazole is thus an acidic and basic substance. Compared to pyrrole, it is more basic and more acidic than pyridine.



1.5 APPLICATIONS OF IMIDAZOLE

Imidazole and its derivatives have various applications in different fields including chemistry, biochemistry, pharmacology and material science. Some of the important applications of imidazole are:

Biological and Medical Applications: Imidazole plays a significant role in numerous crucial biological substances. Notably, histidine, featuring an imidazole side chain, stands

out among them. This amino acid is a component of various proteins and enzymes. (Khalid *et al.*, 2005).

Coordination Chemistry: Imidazole serves as a versatile ligand in coordination chemistry forming stable complexes with metal ions. The ability of imidazole to coordinate to metal is utilized in catalysis and coordination polymer (Abbasi *et al.*, 2017).

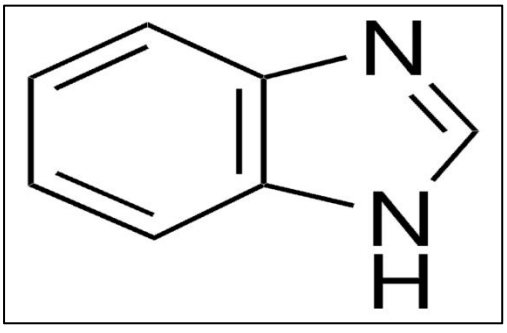
Heterocyclic Chemistry: Imidazole is a key building block in the synthesis of various heterocyclic compounds. It can undergo substitution reaction to form other important heterocycles such as benzimidazole, purine and histidine (Verma *et al.*, 2013).

Supramolecular Chemistry: Imidazole derivatives are often utilized in supramolecular chemistry for their ability to form complexes via hydrogen bonding and coordination interactions, leading to the construction of supramolecular assemblies and functional materials.

These are few examples of the wide range of applications of imidazole and its derivatives. Their versatile nature and diverse properties makes them valuable in many different area of science and technology (Khalid *et al.*, 2005).

1.6 RELATED HETEROCYCLES

1.6.1 Benzimidazole



Benzimidazole, a heterocyclic aromatic organic compound, is a bicyclic structure that can be visualized as the fusion of benzene and imidazole aromatic rings. It presents as white solid tabular crystals.

The production of Benzimidazole involves the condensation of o-phenylenediamine with formic acid or its equivalent, such as trimethyl orthoformate.

$$C_6H_4(NH_2)_2 + HC(OCH_3)_3 \rightarrow C_6H_4N(NH)CH + 3CH_3OH$$

2-Substituted derivatives are obtained when the condensation is conducted with aldehydes in place of formic acid, followed by oxidation.

Benzimidazole is a base:

$$C_6H_4N(NH)CH + H^+ \rightarrow [C_6H_4(NH)2CH]^+$$

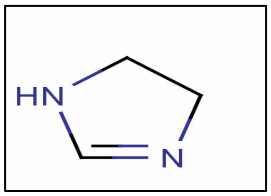
It can also be deprotonated with stronger bases:

$$C_6H_4N(NH)CH + LiH \rightarrow Li[C_6H_4N_2CH] + H_2$$

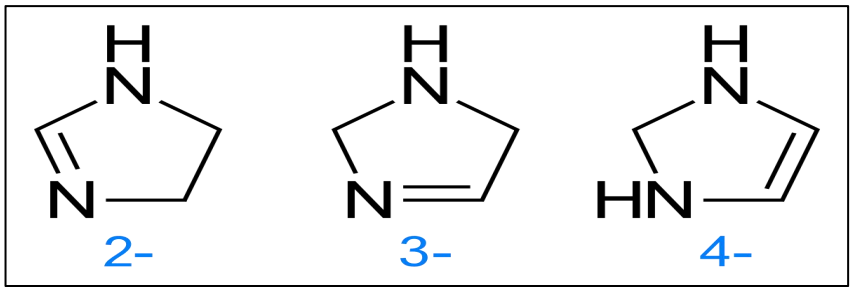
The imine compound has the capability to undergo alkylation and also functions as a ligand in coordination chemistry. A notable benzimidazole complex showcases N-ribosyl-dimethylbenzimidazole, which is commonly found in vitamin B12 (Huynh *et al.*, 2005).

1.6.2 Imidazoline

One of the two double bonds in imidazole is reduced to generate imidazoline, a class of heterocycles. It is known that 2-imidazolines, 3-imidazolines, and 4-imidazolines are the three isomers. Whereas the 4-imidazolines have an alkene group, the 2- and 3-imidazolines have an imine centre. The 2-imidazoline group occurs in numerous drugs (Liu et al., 2009).

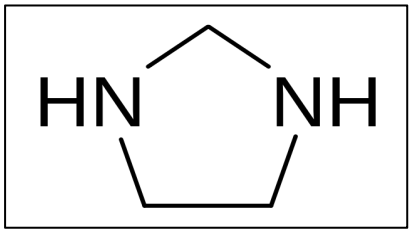


Structure of 2-, 3-, 4-imidazoline:



1.6.3 Imidazolidine

The heterocyclic chemical imidazolidine is (CH2)2(NH)2CH2. Related compounds with one or both nitrogen centres replaced are more prevalent, the parent imidazolidine is investigated less. They are typically polar, basic, colourless molecules. Imidazolidines belong to the general class of aminals and are cyclic compounds with five members (Riebsomer et al., 1954).



1.7 CHEMICAL AND PHYSICAL PROPERTIES OF IMIDAZOLE

Properties	
Chemical formula	$C_3H_4N_2$
Molar mass	68.077g/mol
Appearance	White or pale yellow solid
Density	1.23g/cm^3, solid
Melting point	89 to 91 °C (192 to 196 °F; 362 to 364 K)
Boiling point	256 °C (493 °F; 529 K)
Solubility in water	633g/L
Acidity (pKa)	6.95(for the conjugate acid)
UV-vis (λmax)	206nm
Crystal structure	Monoclinic
Coordination geometry	Planar 5-membered ring

Dipole moment	3.61D
Main hazards	Corrosive

Chemically, imidazole has the formula $C_3H_4N_2$. It is an evaporating white or colorless material that mixes somewhat basically with water. It is an aromatic heterocycle classified in chemistry as a di-azole, with nitrogen molecules not nearby acting as substitutes for one another. Alkaloids in particular contain the imidazole ring, which is present in many chemical molecules. The 1,3- C_3N_2 ring in this imidazole is the same, but its substituent are different. Several essential biological building blocks, notably histidine and the related hormone histamine, contain this ring shape. An imidazole ring is a component of many drugs, including antifungal, nitroimidazole-group antibiotics, and the sedative midazolam (Haynes *et al.*, 2015).

Due to hydrogen's ability to bond with either one or both of the nitrogen atoms, imidazole displays a planar 5-membered ring with two parallel tautomeric forms. Imidazole demonstrates high solubility in water and possesses a dipole moment measuring 3.61 D. It is categorized as aromatic due to its planar ring structure containing six electrons

Imidazole exhibits amphoteric properties, meaning it can act as both an acid and a base. It is slightly less acidic compared to phenols, carboxylic acids, and other imides, but somewhat more acidic than alcohols. The nitrogen-connected proton is the acidic site, leading to the formation of the symmetrical imidazolide anion upon deprotonation. Due to its relatively high pKa as a base (referred to as pKBH+ to avoid confusion), imidazole is approximately sixty times more basic than pyridine, rendering it more reactive. The nitrogen atom with the lone pair serves as the primary site for reactivity. The symmetrical imidazolium cation is created by protonation (Silberberg *et al.*, 2008).

1.8 TOXICOLOGICAL STUDY FOR IMIDAZOLE

1.8.1 Routes for exposure

Imidazole is a chemical compound used in various applications, including pharmaceuticals and as a buffer in biochemistry. Exposure to imidazole can occur through various routes:

1. Inhalation: Imidazole in the form of dust or aerosolized particles can be inhaled if proper safety precautions are not taken when handling it. This can happen in industrial settings where imidazole is used.

2. Skin Contact: Imidazole can be absorbed through the skin, especially if it comes into direct contact with the skin for an extended period. It's important to wear appropriate protective clothing, such as gloves, when handling imidazole.

3.Ingestion: Ingesting imidazole is another route of exposure, which can occur accidentally if there is improper handling or storage of imidazole-containing materials. This is more of a concern in industrial or laboratory settings.

4. Eye Contact: Imidazole can cause irritation if it comes into contact with the eyes. Proper eye protection should be worn when working with imidazole to prevent this type of exposure.

To minimize the risks associated with imidazole exposure, it's important to follow safety guidelines, wear appropriate personal protective equipment, and work with it in well-ventilated areas or under fume hoods in laboratory or industrial settings. Additionally, be sure to wash hands and any exposed skin thoroughly after handling imidazole and seek medical attention if exposure occurs.

1.8.2 Effects of exposure

Exposure to imidazole can have various effects on health, depending on the route and level of exposure. Here are some potential effects:

- Inhalation

Inhalation of imidazole vapors or dust can irritate the respiratory tract, leading to symptoms such as coughing, throat irritation, and difficulty breathing. Prolonged or high-level exposure to imidazole through inhalation in occupational settings may pose a risk of more severe respiratory effects.

- Skin Contact

Direct skin contact with imidazole may cause skin irritation, redness, and in some cases, dermatitis. Allergic reactions or sensitization to imidazole can occur with repeated or prolonged exposure.

- Oral Ingestion

Accidental ingestion of imidazole can lead to symptoms such as nausea, vomiting, abdominal pain, and diarrhea. Ingesting large quantities may result in more severe gastrointestinal effects.

- Eye Contact

Imidazole exposure to the eyes can cause irritation, redness, tearing, and discomfort. Severe exposure may lead to eye injury or damage.

- Dermal Absorption

Imidazole can be absorbed through the skin, potentially leading to systemic effects if a significant amount is absorbed. Symptoms may include headache, dizziness, and in rare cases, more severe systemic effects.

1.8.3 Prevention

1. Use Personal Protective Equipment (PPE): Wear appropriate PPE, including lab coats, gloves, safety goggles, and, if necessary, respiratory protection when working with imidazole.

2. Proper Handling and Storage: Store imidazole in a well-ventilated area away from incompatible chemicals. Follow safety data sheet (SDS) instructions for storage and handling.

3. Ventilation: Ensure good ventilation in areas where imidazole is used or stored to minimize inhalation exposure.

4. Avoid Skin Contact: Minimize skin contact by wearing gloves and lab coats. In case of skin contact, wash the affected area with plenty of water.

5. Eye Protection: Wear safety goggles or a face shield to protect your eyes. In case of eye exposure, flush with water for at least 15 minutes and seek medical attention.

6. Prevent Ingestion: Do not eat, drink, or smoke while working with imidazole. Wash hands after handling.

7. Labeling and Identification: Clearly label containers with imidazole and its hazards. Use appropriate warning labels and signage in the workplace.

1.8.4 First aid

1. Inhalation: If exposed to imidazole vapors and experiencing respiratory distress, move to an area with fresh air. Seek medical attention if breathing difficulties persist.

2. Skin Contact: Remove contaminated clothing and wash the affected skin with plenty of water for at least 15 minutes. If irritation or rash develops, seek medical attention.

3. Eye Contact: Immediately flush the affected eye with water for at least 15 minutes while holding the eyelid open. Seek immediate medical attention.

4. Ingestion: If imidazole is ingested, do not induce vomiting. Rinse the mouth and drink water. Immediately seek medical attention.

5. Allergic Reactions: If an allergic reaction, such as skin sensitization or respiratory distress, occurs due to imidazole exposure, seek prompt medical help (ICSC 1721).

1.9 ISOLATION AND PURIFICATION TECHNIQUES USED

1.9.1 Chromatography

Chromatography is a method employed to separate compounds, facilitating their analysis and examination. It offers insight into the chemical makeup of these compounds. Termed "color writing," chromatography is utilized to test liquid mixtures (Mcmurry et al., 2011).

Chromatography serves as a scientific approach to scrutinize and detect the varied constituents within mixtures of substances or chemicals. This method relies on the differing distribution of components between a stationary phase, often a solid or liquid, and a mobile phase, typically a liquid or gas.

1.9.1.1 Thin-layer chromatography (TLC)

Thin-layer chromatography (TLC) stands as a chromatographic method utilized to segregate constituents within non-volatile compound blends. Its applications encompass compound identification, assessment of sample purity, and related analytical procedures (Jack et al., 2020).

Conducted on a TLC plate comprising an inert solid surface coated thinly with an adsorbent material, termed as the stationary phase, this method involves placing the sample onto the plate. Subsequently, a mobile phase, typically a solvent or solvent blend, is employed to elute the sample, whereby capillary action facilitates the upward movement of this liquid (Xianming et al., 2022).

The separation of compounds occurs due to disparities in their interaction with the stationary phase and their solubility in the solvent. The outcome is quantified by the Retention Factor (Rf), which denotes the ratio of the distance traveled by a particular substance to the distance traveled by the mobile phase (Zhang et al., 2022).

1.9.2 Distillation

Distillation refers to the procedure in which a liquid is transformed into vapor and then condensed back into liquid form. Simple distillation is a technique used to separate mixtures by exploiting variances in their volatility within a boiling liquid blend. By applying heat, the components of a sample mixture are vaporized, and the mixture is rapidly cooled by cold water in a condenser. This method is effective for separating mixtures with notable differences in boiling points among their components (Schaschke et al., 2014).

CHAPTER TWO

2.1 MATERIALS AND METHODS

2.1.1 Materials Used

The apparatus was obtained from the Department of Chemistry, University of Benin, Edo State. They include but not limited to the following:

- Magnetic Stirrer
- Separating Funnel
- Retort Stand
- Clamps
- Hot Plate (Heat Source)
- Beakers
- Measuring Cylinders
- Stopper
- Liebig Condenser
- Vacuum adapter
- T-square neck
- Water Circulator
- Round bottom flasks
- Flat bottom flasks
- Connecting Adapter

- Water Bath
- Containers
- Oven
- Filter papers
- Litmus paper
- Weighing balance
- Spatula

2.1.2 Reagents Used

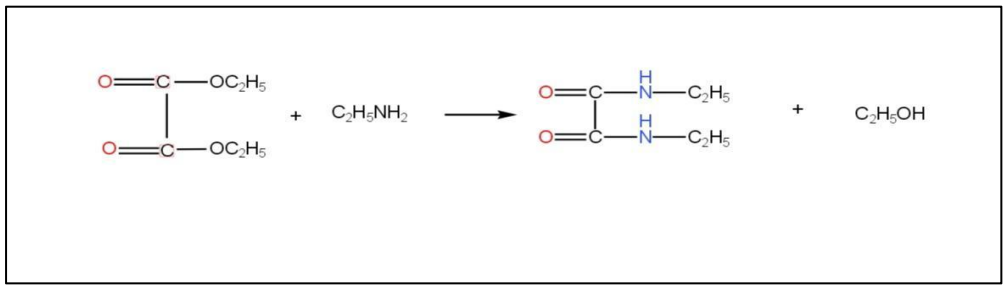
The following were the reagents obtained from obtained from the Department of Chemistry, University of Benin, chemical store and were of analytical grade. They include but not limited to the following:

- Diethyloxalate (Thomas scientific)
- Ethylamine (LOBA Chemie)
- Ethanol (Molychem)
- Phosphorus pentachloride (Wilkinson Vikas)
- Sodium hydroxide pellets (CDH)
- Distilled water
- Chloroform (Molychem)
- Calcium chloride anhydrous (Kernel)
- Concentrated Nitric acid (ReAgent)
- Concentrated Sulphuric acid (JHD ltd)

- Anti-bumping granules
- Sodium bicarbonate
- Thiourea
- Thin-layer chromatography plate

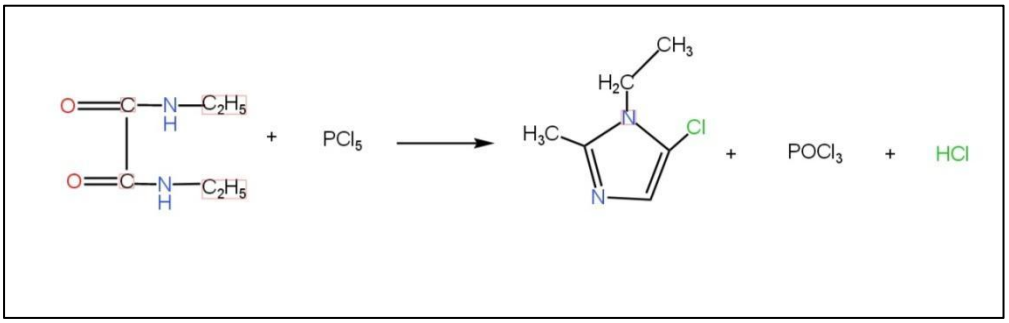
2.2 SYNTHESIS OF 1-ETHYL-2-METHYL-4-NITROIMIDAZOLE-5-THIOL

2.2.1 AMINOLYSIS (SYNTHESIS OF N,N-DIETHYLOXAMIDE)



Ethylamine was added drop wise into a round bottom flasks containing diethyloxalate. The reaction was continuously stirred in crushed ice on a magnetic stirrer until crystals of N,N-diethyloxamide were formed. The crystals were filtered, washed with Ethanol and air dried. The residue obtained after filtration is distilled to obtain more of the product. The weight of the product was 130.6g and the yield was 91.28%.

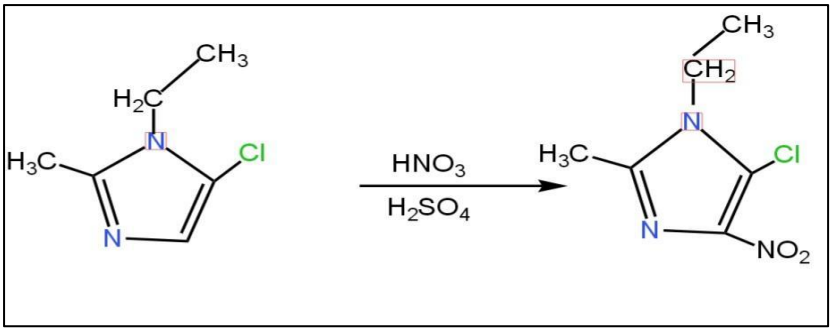
2.2.2 SYNTHESIS OF 5-CHLORO-2-METHYL-1-ETHYLIMIDAZOLE



N,N-diethyloxamide was measured into a round bottom flasks containing phosphorus pentachloride which was fitted with a reflux condenser. The round bottom flask was shaken to mix the two solids. The reaction transpired with the release of copious fumes. After some minutes, the reaction subsided. The resulting yellow liquid was heated for 1 hour continously on a water bath. The water bath was left overnight. The brown liquid was prepared for vacuum distillation to reduce the amount of phosphoryl chloride. After the reduction, it was poured into a cold solution of sodium hydroxide and tested with Litmus paper until strongly alkaline (Neutralization).

Extraction was carried out to obtain a brown liquid which was extracted with chloroform. The extract was washed with chloroform properly and dried using calcium chloride anhydrous. The solvent was filtered, then distilled to give a brown liquid; 1-ethyl-2-methyl-5-chloroimidazole which was measured to be 20.33g and the yield was 87.02%. It was tested using a TLC plate and found to be very pure for the next reaction without further purification.

2.2.3 SYNTHESIS OF 5-CHLORO-1-ETHYL-2-METHYL-4-NITROIMIDAZOLE



In a beaker, compound 2 and concentrated HNO_3 were added and placed on a water bath, the mixture was almost completely evaporated. A concentrated H_2SO_4 solution was added to the contents of the beaker after 2 hours and the mixture was continuously stirred for a few minutes in the cold. Following an hour of heating over a water bath, the mixture was allowed to cool before being poured over crushed ice. After stirring the mixture briefly, it was let to stand. Crystals of 5-chloro-1-ethyl-2-methyl-4-nitroimidazole (compound 3) were precipitated when sodium bicarbonate was added to the solution. The crystals underwent filtering, distilled water washing, air drying and recrystallization for purification. Compound 3 has a melting point of 168 - 170ºC, a mass of 4.65g and a yield of 70.43%.

2.2.4 SYNTHESIS OF 1-ETHYL-2-METHYL-4-NITROIMIDAZOLE-5-THIOL

A cold solution of sodium in 100% ethanol was used to dissolve compound 3. The reaction mixture was exposed to H_2S for four hours. The solution was kept at 50ºC for 12 hours, followed by 4 hours of reflux. After cooling, distilled water was added to the solution to dissolve any solid that had formed, and then strong HCl was added to neutralize it. The precipitate was filtered, cleaned with distilled water, and allowed to dry in the air. The product melting point was 114 - 116ºC and its yield was 70.43%

CHAPTER THREE

3.1 RESULTS AND CONCLUSION

Table 3.1: Physical Properties of the N,N-diethyloxamide

COMPOUND	CHEMICAL FORMULA	MOLAR MASS (g)	COLOUR	NATURE	STATE	MELTING POINT (°C)	YIELD (%)	R_f
N,N′ diethyloxamide	$C_6H_{12}N_2O_2$	144.17	White	Crystalline	Solid	179 - 181	91.28	0.647

Table 3.2: Physical Properties of 5-chloro-1-ethyl-2-methylimidazole

COMPOUND	CHEMICAL FORMULA	MOLAR MASS (g)	COLOUR	NATURE	STATE	BOILING POINT (°C)	YIELD (%)	R_f
5-chloro-1-ethyl-2-methylimidazole	$C_6H_9N_2Cl$	144.60	Brown	Liquid	Liquid	100 - 102	87.02	0.743

Table 3.3: Physical Properties of 5-chloro-1-ethyl-2-methyl-4-nitro imidazole

COMPOUND	CHEMICAL FORMULA	MOLAR MASS (g)	COLOUR	NATURE	STATE	MELTING POINT (°C)	YIELD (%)	R_f
5-chloro-1-ethyl-2-methyl-4-nitro imidazole	$C_6H_8N_3O_2Cl$	189.50	Creamy white	Crystalline	Solid	168 - 170	70.43	0.672

Table 3.4: Physical Properties of the 1-ethyl-2-methyl-4-nitroimidazole 5-thiol

COMPOUND	CHEMICAL FORMULA	MOLAR MASS (g)	COLOUR	NATURE	STATE	MELTING POINT (°C)	YIELD (%)	R_f
1-ethyl-2-methyl-4-nitro imidazole 5-thiol	$C_6H_9N_3O_2S$	187.00	Deep Cream	Powdery	Solid	114 - 116	70.43	0.672

3.1 CONCLUSON

The research study expands our knowledge of the procedure involved in synthesizing 1-ethyl-2-methyl-4-nitroimidazole-5-thiol through a stepwise reaction:

- Reaction of Diethyloxalate with Ethylamine
- Reaction of N,N-Diethyloxamide with Phosphoruspentachloride
- Nitration of 5-chloro-1-ethyl-2-methylimadazole
- Reaction of 5-chloro-1-ethyl-2-methylimadazole with thiourea

Questions which arose include:

- The purity of the synthesized compounds
- The biological significance of the synthesized compounds.